Proposal für einen neuen Forschungsantrag im Rahmen des Membrane lipids as common modulators of neurodegenerative diseases (MELIMOND) Konsortiums (EU Joint Programme – Neurodegenerative Disease Research, Sprecher Jochen Walter).

Genetics, metabolic profiles, and risk of cognitive decline and Alzheimer disease in old age

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Entscheidung der TK: Das Proposal wurde in AgeCoDe/AgeQualiDe TK 5 am 10.03.2014 wie vorgelegt genehmigt. Da die Blutanalysen unter Bonner Schirmherrschaft vorgenommen und im Rahmen der AgeCoDe Fragestellungen ausgewertet werden, sind die unterzeichneten Einverständniserklärungen der Probanden für die angestrebten Auswertungen gültig.

Die Antragsteller werden gebeten die AgeCoDe Study Group über den aktuellen Stand der Anträge und ggf. Projekt auf dem Laufenden zu halten.

Rationale and background:

Sphingolipids (SL) are principal components of biological membranes and exert pleiotropic functions in cellular metabolism, vesicular transport and signal transduction. Although they are ubiquitously expressed in different cell types, SLs display particularly complex and highly specific pattern in neurons. Very rare neurological diseases, grouped as lipid storage disorders (LSDs), are caused by homozygous mutations in genes involved in SL or cholesterol transport and catabolism. These diseases reveal strikingly similar and overlapping clinical and neuropathological phenotypes with the major late onset neurodegenerative disease Alzheimer (AD), including the accumulation and aggregation of characteristic pathogenic proteins, cognitive impairment and severe neurodegeneration. Notably, recent genetic studies showed that several genes involved in metabolism and transport of membrane lipids are among the most common and strongest risk factors for AD.

Objectives:

The present study aims to identify common membrane lipid and protein dependent pathways and mechanisms that underlie the pathogenesis of AD. The overall working hypothesis is that alterations in membrane lipid metabolism and protein homeostasis could drive and modulate common pathways of AD.

Methods:

This project will use state-of-the-art bioinformatic and experimental approaches to investigate the contribution of membrane lipid metabolism and protein homeostasis in common pathogenic pathways of AD. To this end, metabolic profiles will be obtained using a gas chromatography-mass spectrometry (GC-MS), liquid chromatography (LC)-MS, and capillary electrophoresis (CE)-MS. This approach allows detection of more than 2000 targeted metabolites and lipids. This part of the project will be performed in collaboration with the Cornelia van Duijn from Erasmus University MC (EMC) in Rotterdam, The Netherlands. Proteomic profiles will be searched in human sera of Alzheimer patients using a comparative study by LC-MALDI measurements after isobaric isotopic labeling (ITRAQ). A crucial advantage of ITRAQ method is that several samples are measured simultaneously and therefore accounts for methodological variance of a single sample analysis. This part of the project will be performed in collaboration with Franz-Georg Hanisch at University of Cologne, Germany. These profiles will be then combined with genome-wide genotype data from the same AgeCoDe participants in the so-called genome-wide quantitative trait (QT) analysis. To increase genome coverage for the QT analysis, genotype imputation will be performed using the latest 1.000 genome updates.

Expected results:

It became clear that additional, yet unknown, age-depended changes in common metabolic pathways involving lipid and protein metabolism could underlie the pathogenesis of AD. Consequently, this project will generate candidate genetic and epigenetic factors that explain phenotypic variance observed in metabolic and proteomic profiles obtained from AD patients and healthy controls from the AgeCoDe cohort. These genetic and epigenetic may represent promising candidates for modulation of the disease process in AD. Furthermore association between identified genetic and epigenetic variants will be correlated with other endophenotypes assessed within AgeCoDe.

Innovation:

This unique combination and the resulting multi-disciplinary and multi-level approach offer unique opportunities to identify and functionally characterize fundamental disease mechanisms of a major neurodegenerative disease, such as AD. This proposal project will provide great prospects to identify lipid dependent pathways and protein networks relevant for the pathogenesis of AD and potentially for other neurodegenerative diseases. Understanding the similarities and differences in lipid and protein pathology in AD is crucial to identify new clinical phenotypes relevant for targeted therapy.